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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/371,347	08/10/1999	ROY A. GRAVEL	50004/003003	9130

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KRISTINA BIEKER-BRADY
CLARK & ELBING
176 FEDERAL STREET
BOSTON, MA 02110

EXAMINER	
STEADMAN, DAVID J	

ART UNIT	PAPER NUMBER
1652	14

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/371,347	GRAVEL ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5 and 35-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 35-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Application

Claims 1-5 and 35-47 are pending in the application.

Applicants amendment to claims 1 and 3-5, cancellation of claims 6-34, and addition of claims 35-47 in Paper No. 13, filed 09/07/01 is acknowledged.

Applicants' arguments filed in Paper No. 13 have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Drawings

1. The drawings remain objected to by the examiner. It is noted that applicants will submit corrected drawings upon allowance of the application. Direct any inquiries concerning drawing review to the Drawing Review Branch (703) 305-8404.

Claim Objections

2. Claims 36-38 and 41-43 are objected to because of the use of improper sequence identifiers. It is suggested that the term "SEQ ID No.:1" be replaced with, for example, "SEQ ID NO:1".

Claim Rejections - 35 USC § 112

3. Claims 3 and 47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

4. Claim 3 is confusing because any of the listed polynucleotide sequences will not necessarily encode any of the listed polypeptide sequences. It is suggested that applicants clarify the meaning of the claim by inserting "respectively" following "SEQ ID NO:48".

5. Claim 47 is indefinite in the recitation of "a consensus binding site for one or more cofactors". The claim is indefinite because it is unclear as to what constitutes "a consensus binding site for one or more cofactors". It is suggested that applicants clarify the meaning of the claim by, for example, referring to specific nucleotides within the sequences of SEQ ID NOs:1, 41, 43, 45, and/or 47.

6. The written description rejection of claims 1, 2, and 45-47 under 35 U.S.C. 112, first paragraph, is maintained. The rejection was fully explained in a previous Office action. Claims 1 (claims 45-47 dependent therefrom) and 2 are drawn to a polynucleotide encoding a mammalian (claim 1) or human methionine synthase reductase (MSR) polypeptide (claim 2).

Applicants argue that the specification provides a sufficient number polynucleotide sequences encoding wild-type or mutant human MSR polypeptides (SEQ ID NOs:1, 41, 43, 45, and 47), numerous characteristics of mammalian MSR polypeptides, and have provided PCR primer sequences used in the cloning of the human MSR polyeptides that can be used to isolate other mammalian MSR polyeptides. Applicants argue that based on the disclosure of nucleic acids encoding wild-type and mutant human MSR polypeptides (SEQ ID NOs:1, 41, 43, 45, and 47), one of skill in the art could readily identify other mammalian MSR polypeptides based on sequence homology, hybridization, and enzymatic activity.

Applicants' argument is not found persuasive. First, it should be noted that much of applicants' arguments are applicable to the issue of enablement and *not* the instant issue of sufficient written description. Furthermore, although applicants' suggest that all species within the genus of polynucleotides encoding mammalian MSR polypeptides are likely to have significant homology based on the sequence identity (43 %) between human and C. elegans MSR polypeptides, applicants have failed to provide additional members of the genus, i.e., polynucleotides encoding mammalian MSR polypeptides, to sufficiently describe the genus of claimed polynucleotides. The specification fails to provide a sufficient description of the claimed genus of polynucleotides encoding MSR polypeptides as it merely describes the

functional features of the genus without providing any definition of the structural features of the species within the genus. The CAFC in *UC California v. Eli Lilly*, (43 USPQ2d 1398) stated that: "In claims to genetic material, however a generic statement such as 'vertebrate insulin cDNA' or 'mammalian insulin cDNA', without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore, cannot as one can do with a fully described genus, visualize or recognize the identity of the members of the genus". Similarly with the claimed genus of polynucleotides encoding mammalian MSR polypeptides, the functional definition of the genus does not provide any structural information commonly possessed by members of the genus which distinguish the polynucleotide species within the genus from other polynucleotides such that one can visualize or recognize the identity of the members of the genus. Therefore, applicants have not fully described the claimed polynucleotides.

7. The written description of claims 4, 5, and 35-47 under 35 U.S.C. 112, first paragraph, is maintained. The rejection was fully explained in a previous Office action.

Claims 4, 5, 35, 36 (claims 37, 38, 45-47 dependent therefrom), 39-41 (claims 42, 43, and 45-47 dependent therefrom), and 44 are drawn to a polynucleotide that hybridizes to a sequence within SEQ ID NOs:1 or 41, wherein the sequence comprises a naturally-occurring mammalian MSR mutation or polymorphism (claim 4), and optionally wherein the polynucleotide is complementary to at least 50 % of at least 60 nucleotides of SEQ ID NOs:1 or 41 (claim 5), and optionally wherein the mutation is selected from claim 35, a polynucleotide that has at least 50 % sequence identity to SEQ ID NO:1 (claim 36), and optionally wherein the polynucleotide comprises a naturally-occurring mammalian MSR mutation or polymorphism (claim 39), and optionally wherein the mutation is selected from claim 40, or a polynucleotide that has at least 50 % sequence identity to a region of SEQ ID NO:1, wherein the polynucleotide comprises a naturally-occurring mammalian MSR mutation or polymorphism (claim 41), and optionally wherein the mutation is selected from claim 44.

Applicants argue that three species of polynucleotides that hybridize to SEQ ID NOs:1 or 41 (SEQ ID NOs:43, 45, or 47) have been provided in the specification and therefore, the claimed genus of polynucleotides have been sufficiently described. Applicants' argument is not found persuasive. As stated in the previous Office action, the genus of polynucleotides that comprise the claimed nucleic acid molecules is a *large variable genus* with the potentiality of encoding many different proteins. Therefore, many functionally unrelated polynucleotides are encompassed within the scope of the claimed genus of nucleic acids. The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. A representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. Satisfactory disclosure of a representative number depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. For inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only three species within the genus. The genera of claimed polynucleotides encompasses widely variant species including polynucleotides encoding polypeptides that have MSR activity, lack activity but are capable of inducing an antibody, an enormous number of polypeptides with neither of these functions, but possibly having other undisclosed functions, as well as polynucleotides that function as PCR primers or hybridization probes. As such, neither the description of the structure and function of SEQ ID NOs:1, 41, 43, 45, and 47 nor the disclosure of solely structural features present in all members of the genus is sufficient to be representative of the attributes and features of the entire genus. Therefore, applicants have not fully described the claimed polynucleotides.

8. The enablement rejection of claims 1, 2, 4, 5, and 35-47 under 35 U.S.C. 112, first paragraph, is maintained. The rejection was fully explained in a previous Office action.

Claims 1, 2, 4, 5, 35, 36 (claims 37 and 38 dependent therefrom), 39-41 (claims 42 and 43 dependent therefrom), and 44-47, while being enabling for the polynucleotides of SEQ ID NOs:1, 41, 43, 45, or 47, does not reasonably provide enablement for *any* polynucleotide encoding a mammalian (claim 1), and optionally having at least 20-30 % (claim 45) or 55-75 % (claim 46) of the activity of SEQ ID NO:2, and optionally encoding a mammalian MSR polypeptide comprising a consensus binding site for one or more of FAD, FMN, and NADPH (claim 47), *any* polynucleotide encoding a human methionine synthase reductase (MSR) polypeptide (claim 2), *any* polynucleotide that hybridizes to a sequence within SEQ ID NOs:1 or 41, wherein the sequence comprises a naturally-occurring mammalian MSR mutation or polymorphism (claim 4), and optionally wherein the polynucleotide is complementary to at least 50 % of at least 60 nucleotides of SEQ ID NOs:1 or 41 (claim 5), and optionally wherein the mutation is selected from claim 35, *any* polynucleotide that has at least 50 % sequence identity to SEQ ID NO:1 (claim 36), and optionally wherein the polynucleotide comprises a naturally-occurring mammalian MSR mutation or polymorphism (claim 39), and optionally wherein the mutation is selected from claim 40, and optionally having at least 20-30 % (claim 45) or 55-75 % (claim 46) of the activity of SEQ ID NO:2, and optionally encoding a mammalian MSR polypeptide comprising a consensus binding site for one or more of FAD, FMN, and NADPH (claim 47), or *any* polynucleotide that has at least 50 % sequence identity to a region of SEQ ID NO:1, wherein the polynucleotide comprises a naturally-occurring mammalian MSR mutation or polymorphism (claim 41), and optionally wherein the mutation is selected from claim 44 and optionally having at least 20-30 % (claim 45) or 55-75 % (claim 46) of the activity of SEQ ID NO:2, and optionally encoding a mammalian MSR polypeptide comprising a consensus binding site for one or more of FAD, FMN, and NADPH (claim 47).

Applicants argue that the claims are fully enabled as evidenced by the usefulness of the claimed nucleic acids, including fragments and variants of SEQ ID NO:1 or 41 as encompassed by the claims, in a plurality of applications and that given such applications, it would be unfair to limit applicant to nucleic

acids encoding an active MSR polypeptide. Applicants further argue that claims 45-47 have further limited the claimed polynucleotides by rectiting specific functional limitations (having at least 20-30 % or 55-75 % of the activity of SEQ ID NO:2) or a structural limitation (comprising a consensus binding site for one or more of FAD, FMN, and NADPH). This is not found persuasive because applicants have not provided guidance as to methods of making and/or isolating *any* nucleic acid encoding a mammalian or human MSR polypeptide, or the nucleic acids as set forth in claims 1, 36, or 41 with at least 20-30 % or 55-75 % of the activity of SEQ ID NO:2 or encoding a mammalian MSR polypeptide comprising a consensus binding site for one or more of FAD, FMN, and NADPH. At the time of the invention, the prior art disclosed no mammalian or human polynucleotides encoding MSR polypeptides, nor methods of isolating such polynucleotides. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has not been provided in the instant specification, and therefore screening for all possible nucleic acids encoding mammalian or human MSR polypeptides or the nucleic acids as set forth in claims 1, 36, or 41 with at least 20-30 % or 55-75 % of the activity of SEQ ID NO:2 or encoding a mammalian MSR polypeptide comprising a consensus binding site for one or more of FAD, FMN, and NADPH as encompassed in the claims would clearly constitute undue experimentation.

Furthermore, the functional activity of an encoded polypeptide is dependent on the structure of the encoding polynucleotide. A fragment of a polynucleotide encoding a polypeptide with a specific function will not necessarily retain similar activity if found within a larger polynucleotide. Similarly, a variant of a polynucleotide encoding a polypeptide with a specific function will not necessarily retain similar activity. The contexts in which activity of a polynucleotide comprising a nucleic acid fragment or a variant of a polynucleotide will be maintained are highly unpredictable and the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful. Furthermore, while methods to isolate functional fragments and variants of a known sequence are well known to the skilled artisan, producing functional fragments or variants as claimed by applicants requires

one of skill in the art to know or to be provided with guidance for the selection of which of the infinite number of fragments or variants retain enzymatic activity. Without such guidance one of skill would be reduced to the necessity of producing and testing all of the claimed fragments or variants as encompassed by the claims for enzymatic activity. As stated above, this would clearly constitute undue experimentation. Therefore, applicants have not fully enabled the claimed polynucleotides.

Conclusion

9. No claim is in condition for allowance. All claims are rejected.

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (703) 308-3934. The examiner can normally be reached Monday-Friday from 8:00 am to 4:30 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX number for this Art Unit is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

David J. Steadman, Ph.D.

Rebecca Prouty

REBECCA E. PROUTY
PRIMARY EXAMINER
GROUP ~~1800~~ 1600